Familial Aggregation and Heterogeneity of Non-Hodgkin Lymphoma in Population-Based Samples

Lynn R. Goldin,[1] Ola Landgren,[1] Mary L. McMaster,[1] Gloria Gridley,[2] Kari Hemminki,[4,5] Xinjun Li,[5] Lene Mellemkjaer,[6] Jørgen H. Olsen,[6] and Martha S. Linet[3]

[1]Genetic Epidemiology Branch, [2]Biostatistics Branch, [3]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [4]Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany; [5]Department of Biosciences at Novum, Karolinska Institute, Stockholm, Sweden; and [6]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Abstract

The importance of genetic factors in the etiology of non-Hodgkin lymphoma (NHL) is suggested by case-control and cohort studies. Most previous studies have been too small to estimate accurately risks of specific categories of lymphoproliferative malignancies in relatives of NHL cases or to quantify the contribution of NHL case characteristics to familial risk. We have overcome sample size limitations and potential recall bias by using large databases from Sweden and Denmark. Diagnoses of lymphoproliferative malignancies were compared in 70,006 first-degree relatives of 26,089 NHL cases (including 7,432 with subtype information) versus 161,352 first-degree relatives of 58,960 matched controls. Relatives of NHL cases were at significantly increased risk for NHL [relative risk (RR), 1.73; 95% confidence interval (95% CI), 1.39-2.15], Hodgkin lymphoma (RR, 1.41; 95% CI, 1.0-1.97), and nonsignificantly for chronic lymphocytic leukemia (CLL; RR, 1.31; 95% CI, 0.93-1.85). No increased risk was found for multiple myeloma among case relatives. Findings with respect to siblings compared with parents and offspring or with respect to age at diagnosis of proband were inconsistent. In both populations, relatives of cases with an aggressive NHL subtype were at substantially increased risk of NHL (combined RR, 3.56; 95% CI, 1.80-7.02). We conclude that NHL has an important familial component, which is shared with Hodgkin lymphoma and CLL. We estimate that the absolute lifetime risk for a first-degree relative of an NHL case to develop NHL is 3.6% (compared with a population risk of 2.1%) and higher if the index case had an aggressive subtype of NHL. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2402–6)

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies that represents the most frequently occurring major category within the rubric of lymphoproliferative malignancies. The American Cancer Society has projected that >56,000 cases will be diagnosed in the United States in 2005 (1). The annual incidence rate increased by about 80% from 1975 to 1995 in the United States, although rates seemed to have remained stable since then (2). Similar trends have been seen in other Western countries (3). Males are more frequently affected than females, and Whites have higher rates than Blacks and Asians. Immunodeficiency (including HIV) and immunosuppression are strong risk factors for NHL. Other possible risk factors include other viruses, history of certain autoimmune disorders, and agricultural exposures (2, 3).

Case-control (4-7) and cohort studies (8-11) have consistently shown significantly increased risks of NHL (range, 2.0-4.0) associated with a family history of lymphoma or other hematopoietic malignancy. Due to the sample size limitations of most case-control studies and the limitations of recall about a relative's cancer by an index subject, little is known with regard to the spectrum of lymphoproliferative malignancies that aggregate with NHL or differences in familial risk for subtypes of NHL. In our study, we used a case-control design to compare the risks of lymphoproliferative tumors in first-degree relatives of patients with NHL (including subtypes in over 7,000 cases) with the risks in first-degree relatives of matched controls. We applied a survival analysis approach that accounted for correlation among related individuals, truncation in the data due to start dates of cancer registrations, and complete ascertainment of all NHL cases in the population (12). Our model also incorporated heterogeneity in aggregation by the relative's gender and relationship to the case and by the case's age at diagnosis. In this largest study to date, including data from both Sweden and Denmark up to a 40-year period, we have been able to quantify more precisely than in other studies the degree of familial aggregation of NHL and related lymphoproliferative malignancies.

Materials and Methods

The Swedish Family-Cancer Database has been described previously (13-15). Briefly, Sweden maintains a multigeneration register consisting of individuals born in 1932 and later with links to their parents using the unique national registration numbers for all individuals. The multigeneration registry was electronically merged with the Swedish Cancer Registry (all cancers, 1958-1998) to create the Family-Cancer Database. Demographic and vital status information was obtained by linking the Family-Cancer Database to the nationwide census and death notification databases, respectively. The completeness of this database has been described in detail (13) and includes 75% of all tumors registered in the Swedish Cancer registry. We selected from the Swedish Family-Cancer Database all individuals with a first primary diagnosis of NHL (ICD7 = 200× and 202×) occurring between 1958 and 1998. For each case, two cancer-free controls matching the case in gender, year of birth, and county of residence were chosen from the Family-Cancer Database. For each case and control, all first-degree relatives were included

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Note: The Swedish Family-Cancer Database was created by linked registers maintained at Statistics Sweden and the Swedish Cancer Registry.

Requests for reprints: Lynn R. Goldin, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, MSC 7236, Bethesda, MD 20892-7236. Phone: 301-402-9656; Fax: 301-402-4489. E-mail: goldinl@mail.nih.gov

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in the data set. Duplicate control individuals were dropped. We analyzed data for 19,651 NHL probands and their 54,627 first-degree relatives and 38,981 control probands and their 108,969 first-degree relatives.

A similar database of NHL cases, controls, and relatives was created (14, 15) using the Danish Cancer Registry and the Danish Central Population Registry (CPR). All cases of NHL diagnosed from 1968 to 1997 (as either a first or second primary) were selected from the Cancer Registry. Four matched (by gender and year of birth) cancer-free controls per case were chosen from the CPR. All first-degree relatives of cases and controls were identified by linking the unique individual IDs of the subjects to the CPR. The CPR contains links of offspring to parents (and vice versa) starting with all children born in 1968 as well as linkages among family members who were living in the same address in 1968. The unique IDs of the relatives were then electronically linked to the Cancer Registry to obtain all cancer diagnoses. Cases and controls with no linkable relatives were dropped and duplicate controls were also dropped. This caused the number of control probands per case to vary. Approximately 37% of cases and controls could be linked to relatives. We analyzed data for 6,438 NHL probands and their 15,379 first-degree relatives and 19,979 control probands and their 52,383 first-degree relatives. Approximately 95% of the case probands had NHL as a first primary tumor, making this sample comparable with the Swedish sample.

Statistical Analysis. The statistical approach is based on a model proposed by Liang (16) and described in detail elsewhere (12). We classified relatives as ''affected'' if they had a first, second, or third primary cancer registration with the tumor of interest. Here, the age or age at onset of disease in a relative of a proband is modeled by a proportional hazards model. Familial aggregation for each condition is evaluated by testing the hazard ratio of being a relative of a case compared with a relative to a control. The model was fitted to the data using the PHREG procedure in SAS v8.02. We use relative risk (RR) to denote the hazard ratio defined above. The robust sandwich covariance matrix accounts for the dependence of the family members. We tested separately for increased risk for NHL, Hodgkin lymphoma, chronic lymphocytic leukemia (CLL), and multiple myeloma in relatives and also tested for increased risk of developing *any* one of the four tumors considered as a combined entity. Data were analyzed for each population both separately and pooled together. Because case and control probands were matched for risk factors thought to be important for NHL, the relatives should be generally well matched. However, because they cannot be individually matched, we adjusted for gender in all analyses and for country when samples were combined. Because strong secular trends affected the population incidence rates for NHL during the time period of this study (2, 3), birth cohort (using 1941 as a cutoff) was used as a proxy for secular trends. The main effect of interest in this analysis is the increased risk associated with being a relative of a case compared with being a relative of a control. However, we were also interested in testing whether other factors such as gender, type of relative, age of disease onset in the case proband, or histologic subtype affected case-control comparisons. Thus, we analyzed the data both by stratifying on these factors and by testing them as interaction effects in one model. Age at diagnosis was stratified at <50 versus ≥50 and <65 versus ≥65 to be consistent with other published studies. The classification by histologic subtype is more complicated, because NHL is a heterogeneous group of entities, and etiologies are known to be different for some subtypes. For over 7,000 of the more recently diagnosed cases, additional histopathology codes (Systemized Nomenclature of Medicine codes in Sweden starting in 1993 and International Classification of Diseases for Oncology in Denmark starting in 1978) were available and we used these to subset the cases into three categories: low-grade B NHL (the most numerous being follicular lymphoma), high-grade B NHL (mainly diffuse large B cell lymphoma), and T-cell and anaplastic large cell NHL. This categorization was originally derived from the Kiel classification (ref. 17; which was applied by most pathologists in Sweden and Denmark during a major part of the actual study period) and which was later developed and refined in the REAL and most current WHO classifications (18). In this study, we use the terms ''aggressive'' and ''indolent'' to denote high-grade and low-grade B-cell NHLs, respectively. Many studies include CLL as an indolent lymphoma. However, we have analyzed relatives of CLL cases previously (14) as a separate group; thus, they are not included here. There are data in the literature suggesting increased sex concordance in Hodgkin lymphoma and CLL sib pairs (19, 20). We tested whether the gender concordance in our samples of NHL-NHL sib pairs differed from random expectations.

Results

Sample Characteristics. The cases in our samples were diagnosed over a long period of time, but the age and gender distribution of the cases is comparable with other studies (Table 1). The majority of cases in both countries were diagnosed during the last two decades of the time period available. In Denmark, the cases were younger, but this is probably due to the fact that younger cases were more likely to be linkable to relatives. The higher proportion of males in Denmark compared with Sweden is consistent with this younger age distribution. Histologic subtype was available for 20% and 55% of the cases in Sweden and Denmark, respectively.

Table 1. Description of NHL cases

	Sweden				Denmark			
	All	<65 y	≥65 y	Males	All	<65 y	≥65 y	Males
Total number, *n* (%)	19,651	10,110 (57)	9,541 (43)	11,220 (57)	6,437	5,233 (81)	1,204 (19)	3,971 (62)
Year of diagnosis, *n* (%)								
1958-1967	1,276 (6)							
1968-1977	2,906 (15)				620 (10)			
1978-1987	5,620 (29)				1,753 (27)			
1988-1998	9,849 (50)				4,064 (63)			
Histologic subtypes*								
Indolent	2,480 (13)	1,122 (45)	1,358 (55)	1,290 (52)	2,034 (32)	1,647 (81)	387 (19)	1,179 (58)
Aggressive	1,054 (5)	452 (43)	602 (57)	568 (54)	1,248 (19)	974 (78)	274 (22)	770 (62)
T-cell/anaplastic large cell	351 (2)	178 (51)	173 (49)	209 (59)	263 (4)	185 (70)	78 (30)	183 (69)
Unclassified	15,766 (80)	8,358 (53)	7,408 (47)	9,153 (58)	2,892 (45)	2,427 (84)	465 (16)	1,839 (64)

*See Materials and Methods for definition of subtypes.

Table 2. Numbers of affected relatives and RRs for development of lymphoproliferative tumors based on survival analysis of case versus control relatives

Category of relative	Sweden			Denmark			Combined samples, RR (95% CI)
	Case relatives	Control relatives	RR (95% CI)	Case relatives	Control relatives	RR (95% CI)	
Total number of relatives	54,627	108,969		15,379	52,383		
Parents	8,419	16,233		2,162	8,301		
Sibs	7,479	14,978		1,519	5,560		
Offspring	38,729	77,758		11,415	37,598		
Affected relatives							
NHL total, *n* (%)	193 (0.353)	214 (0.196)	1.80 (1.42-2.29)	23 (0.149)	51 (0.097)	1.51 (0.81-2.82)	1.73 (1.39-2.15)
HL total, *n* (%)	47 (0.086)	63 (0.057)	1.48 (1.01-2.18)	11 (0.071)	27 (0.051)	1.31 (0.65-2.65)	1.41 (1.00-1.97)
CLL total, *n* (%)	46 (0.084)	70 (0.064)	1.32 (0.91-1.91)	6 (0.039)	16 (0.030)	1.35 (0.53-3.45)	1.31 (0.93-1.85)
MM total, *n* (%)	49 (0.089)	86 (0.079)	1.15 (0.81-1.63)	1 (0.006)	15 (0.029)	0.23 (0.03-1.74)	1.06 (0.75-1.48)
Any LP, total, *n* (%)	332 (0.607)	430 (0.394)	1.55 (1.31-1.82)	41 (0.266)	108 (0.206)	1.27 (0.84-1.93)	1.48 (1.27-1.72)

NOTE: Any lymphoproliferative tumor was defined as any one of the four tumors. All analyses were adjusted for sex, birth cohort (for NHL, any lymphoproliferative), and country.
Abbreviations: HL, Hodgkin lymphoma; LP, lymphoproliferative; MM, multiple myeloma.

Familial Risks. Table 2 shows the numbers and types of first-degree relatives that were linkable to NHL cases. In both populations, offspring make up the largest group, which is not surprising given the late onset of NHL. The table also shows the numbers (and percentages) of lymphoproliferative cases in case and control relatives in the two populations and the RRs computed from survival analysis. In Sweden, first-degree relatives of NHL cases were at highest risk for developing NHL [RR, 1.80; 95% confidence interval (95% CI), 1.42-2.29], but the risk of Hodgkin lymphoma was also significantly increased (RR, 1.48; 95% CI, 1.01-2.18). The risk of CLL was increased but was not significant (RR, 1.32; 95% CI, 0.91-1.91). In Denmark, the pattern of the findings was similar, but none of the risks were significantly different from 1.0. In the combined data, RRs were significantly increased for NHL (RR, 1.73; 95% CI, 1.39-2.15) and Hodgkin lymphoma (RR, 1.41; 95% CI, 1.00-1.97) and nonsignificantly increased for CLL (RR, 1.31; 95% CI, 0.93-1.85). The RR for multiple myeloma was close to 1.0. RR for ''any lymphoproliferative tumor'' was significantly increased in Sweden (RR, 1.55; 95% CI, 1.31-1.82) and in the combined data (RR, 1.48; 95% CI, 1.27-1.72). As expected from population rates, gender was a significant covariate in most of the analyses. Birth cohort was a significant covariate for NHL and ''any lymphoproliferative tumor.'' The RR estimates in Table 2 were adjusted for these factors, but because our samples were well matched, the adjustments had a negligible effect on the estimates.

When the samples were stratified by gender of relative, siblings versus parents or offspring, or age at diagnosis of proband (or when the factors were tested as interaction effects), there were almost no significant differences in familial risk of developing each of the lymphoproliferative malignancies due to these factors. The two exceptions were that the risk for CLL in Sweden and in the combined data was affected by whether the proband was diagnosed before 50 versus 50 or older (combined data interaction: RR, 1.92; 95% CI, 1.04-3.52) with RR being significantly >1.0 among relatives of late onset probands (RR, 1.60; 95% CI, 1.04-2.47). The risk for ''any lymphoproliferative tumor'' in Denmark was affected by whether the relative was a sibling or not (interaction: RR, 3.16; 95% CI, 1.15-8.69) with RR being significantly >1.0 in siblings of cases (RR, 4.29; 95% CI, 1.26-14.64).

The strongest finding in this study was a much higher familial risk among relatives of probands with aggressive NHL compared with those with indolent NHL or to the overall population. Whereas these differences were not statistically significant, they were consistent in the two populations. The combined RR of NHL was 3.56 (95% CI, 1.80-7.02) among relatives of cases with aggressive NHL, about 2-fold higher than the overall risk of 1.73 for risk of NHL in all relatives combined from both populations; a similar increase was seen in both populations (Sweden RR, 3.07; 95% CI, 1.29-7.31; Denmark RR, 4.33; 95% CI, 1.54-12.13). The combined RR of NHL in relatives of indolent cases was 1.41 (95% CI, 0.91-2.18; not significant) and was similar in the two populations. Sample sizes of relatives of cases with T-cell/anaplastic large cell NHL were too small to draw conclusions.

To test for increased sex concordance among siblings with lymphoproliferative tumors, we analyzed within the combined sample, the 15 families where two siblings had a diagnosis of NHL. This is a small number of families given the large sample of relatives available and is likely due to the fact that siblings of cases comprised only 13% of the sample. Nonetheless, the sex concordance distribution was extremely distorted among these sib pairs. Among the 15 pairs, there were six male-male, eight female-female, and one male-female. Assuming the observed gender ratio of our sample (58% males), there was no excess of male-male pairs but a large excess of female-female pairs and a shortage of mixed gender pairs. This distribution is significantly different from that expected under the null ($\chi^2 = 16.81$, 2 degrees of freedom, $P = 0.0002$).

Discussion

In a combined sample from both populations, first-degree relatives of NHL cases were at highest risk for NHL but were also at significantly increased risk for Hodgkin lymphoma. The risk for CLL was increased but was not significant. This is consistent with our previous findings that relatives of Hodgkin lymphoma and CLL cases in Sweden and Denmark (14, 15) were at increased risk for NHL. Some aggregation of Hodgkin lymphoma and NHL in particular may be due to misclassification of these two tumor types (21, 22). However, common etiology is also implied from second cancer studies in which cases with Hodgkin lymphoma are at increased risk of developing NHL (23-25), from cases where Hodgkin lymphoma and NHL coexist in the same tumor (26), and from our detailed genetic studies of high-risk families, among whom different lymphoproliferative malignancies occur within the same family (27, 28). We found no increased risk of multiple myeloma among relatives of NHL cases, which is consistent with our analyses of similar Swedish data showing that relatives of multiple myeloma cases were at increased risk for multiple myeloma but not other lymphoproliferative malignancies.[7] There were no gender differences in familial risk. Siblings were at higher risk for NHL and Hodgkin

[7] Unpublished data.

lymphoma than other relatives, but this was not significant in the combined data. Increased risk of NHL due to an affected sibling has been reported in some (5, 7, 8) but not all (6) studies. A higher risk in siblings could be due to recessive genes or to environmental factors shared by siblings.

We found a substantially increased risk of NHL in relatives of cases with aggressive NHL compared with relatives of all NHL cases (or compared with relatives of indolent NHL cases) in both populations. This finding is consistent with Vachon et al. (29) who reported that familial NHL cases were more likely to have an aggressive subtype than were sporadic NHL cases. Pottern et al. (5) found a significantly elevated risk of diffuse NHL among subjects who had a sibling with lymphoma in an earlier case-control study of lymphoproliferative malignancies conducted in Iowa and Minnesota. In contrast, a recent multicenter U.S. case-control study of NHL in the state of Iowa and in metropolitan regions of Los Angeles, Seattle, and Detroit found an increased risk of NHL in relatives of cases with follicular lymphoma cases but not in relatives of cases with diffuse large B-cell lymphoma (7). A restricted analysis of the last 10 years in Sweden showed evidence of parent-offspring concordance for NHL subtypes, but the numbers were extremely small (11). If the increased familial risk of aggressive tumors is confirmed, then this has important implications for design of genetic studies.

Early age at diagnosis of cancer is often found to distinguish subtypes with higher genetic susceptibility. In our samples, age at diagnosis of the NHL case was not a strong or consistent predictor of risk in relatives. In Sweden, there was a higher risk of NHL among relatives of cases diagnosed at age $\geq$65 years, which was not significant but is consistent with other reports in the literature (6, 7, 9). We found no difference in age at diagnosis of those relatives who developed NHL among NHL cases versus controls and no clustering of childhood onset NHL in relatives of cases (data not shown). Other investigators have reported that there is anticipation (earlier age at diagnosis of NHL in offspring than in their parents who developed NHL) in age at diagnosis of NHL in high risk families (30). We recently analyzed our data for anticipation and found that after taking into account secular trends in incidence rates of NHL, there was no evidence for earlier age at diagnosis in offspring compared with parents (31).

Our sample had a highly skewed gender distribution of NHL-NHL sib pairs with an excess of female-female pairs and a shortage of mixed gender pairs. There have been reports of increased sex concordance of sib pairs with Hodgkin lymphoma (19) and CLL (20) and some have speculated that some of this excess could be due to genes in the pseudoautosomal region of the X chromosome (32, 33). Despite our large samples of relatives, the numbers of sib pairs with NHL was small; thus, further studies are needed to confirm the observed increased gender concordance.

The Swedish Family-Cancer Database is known to be incomplete for individuals born before 1991 (13). To eliminate this possible survivor bias in estimates of familial aggregation, we repeated the analysis of NHL in relatives of Swedish cases compared with controls based only on outcomes from 1991 and later. The RR was very close to that computed when all the data were included and was highly significant (results not shown). This should not be a bias in Denmark, because our cases were ascertained starting at the same time (1968) that the CPR began to register offspring and parent linkages. It is encouraging that despite the changes over time in definition and classification of NHL, there is strong evidence of familial aggregation regardless of the time period considered.

As large-scale genomic studies have become feasible, there is the opportunity to identify genes from pathways likely to be relevant to lymphoma development and then test for associations of these gene polymorphisms with NHL in case-control studies. For example, some associations between gene polymorphisms involved in immune function (34) and DNA repair (35) and risk of NHL have been reported. This is an exciting emerging area of research, but because the number of potential candidates is large, findings may be hard to replicate. Given the significant familial aggregation of NHL and related conditions, a complementary approach to detecting susceptibility genes would be to conduct whole genome linkage studies in samples of high-risk families.

The clinical significance of increased risk to relatives is modest but not trivial. The lifetime risk of NHL based on the Surveillance Epidemiology and End Results data is 2.1% (1). The RRs we found (Table 2) predict a risk of 3.6% for NHL and a 5% risk for any lymphoproliferative malignancy in first-degree relatives of NHL cases. The lifetime risk for NHL may be even higher if the case proband had an aggressive NHL, but only a small proportion of our samples of cases could be classified into subtypes.

In conclusion, our data quantify the small yet important familial component of NHL, which also encompasses other B-cell malignancies. In addition to this broad familial aggregation, we found that aggressive histologic subtypes of NHL are associated with a higher degree of familial risk.

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